Public Health England

Protecting and improving the nation's health

Epidemiology and management of major salivary gland cancers

National Cancer Registration and Analysis Service

About Public Health England

Public Health England exists to protect and improve the nation's health and wellbeing, and reduce health inequalities. It does this through world-class science, knowledge and intelligence, advocacy, partnerships and the delivery of specialist public health services. PHE is an operationally autonomous executive agency of the Department of Health.

Public Health England
Wellington House
133-155 Waterloo Road
London SE1 8UG
Tel: 020 7654 8000
www.gov.uk/phe
Twitter: @PHE_uk
Facebook: www.facebook.com/PublicHealthEngland

Prepared by: Rebecca Girdler, National Cancer Registration and Analysis Service (NCRAS), Public Health England
Edward Odell, Professor of Oral Pathology and Medicine, King's College London and Honorary Consultant Guy's and St Thomas' NHS Foundation Trust
Graham Putnam, Consultant Oral and Maxillofacial Surgeon, North Cumbria University Hospitals NHS Trust, Chair Head & Neck Cancer Site Specific Clinical Reference Group

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Contents

About Public Health England 2
Introduction 4
Background 4
Method 5
Results 6
Examination of histological classification 6
Conclusions 26
References 28
Appendix 29

Introduction

The incidence of major salivary gland cancer has increased in England but the reasons for this are unclear. This report aims to examine the epidemiology of incidence trends by age, sex, histological type, deprivation and ethnicity of major salivary gland cancers in England. This report also provides a descriptive overview of the current management and survival of patients with these rare types of head and neck cancer.

Background

Major salivary gland cancer is a rare disease accounting for 0.2% of all malignant neoplasms and 9% of head and neck cancers registered in England from 2009 to 2013[1]. Trends in audit data for England and Wales have highlighted an increasing incidence but the reasons for this increase are unclear[2,3]. In the last few years there have been around 600 new cases of major salivary gland cancer registered annually in England and the incidence rate was 1.25 per 100,000 persons in 2009 to 2013. International comparisons are difficult to draw due to differences in definitions but incidence rates range from 0.6 to 1.2 but with little evidence of incidence rises in other countries. [4,5,6,7]

There are three main pairs of major salivary glands: the parotid, submandibular and sublingual glands. Additionally, there over 600 minor salivary glands across the surface of the mouth and throat. Most cases present as a painless, enlarging lump although patients can also experience numbness or muscle weakness on one side of the face, or pain and difficulties in swallowing or opening the mouth. Around 80% of neoplasms occur in the parotid glands and three quarters of these are benign, about 10% occur in the submandibular glands with the rest occurring in the sublingual and minor glands. Due to limitations in recording and classification, cases that are in situ, benign, or of the minor salivary glands are not included in the scope of this report.

Salivary gland cancers comprise a diverse group of differing histological types. Due to the anatomy of the salivary glands, their close proximity to other head and neck sites and the presence of lymph glands in the parotid, skin cancers, cancers of adjacent head and neck sites, or cancers on distant sites can spread into the salivary glands by direct invasion or distant metastasis. So a proportion of cancers found in the salivary glands are not *de novo*, or novel primary tumours that have arisen in the salivary glands[6,8]. This, along with the rarity of the disease, makes the classification, treatment and understanding of major salivary gland cancers and their development challenging.

Method

Diagnoses of 11,432 new malignant salivary gland cancer from 1990 to 2013 were taken from the English national cancer registry's cancer analysis system. Cases were included from the three pairs of major salivary glands: the parotid (C07), submandibular (C080) and sublingual (C081) glands plus overlapping and unspecified major salivary glands (C088 and C089) as defined by the International Classification of Diseases for Oncology version 3 (ICD-O-3) anatomical site codes.

Cases were joined with the National Head and Neck Cancer Audit dataset as this captures additional details about patient assessment and management of the patient care pathway. The audit has collected annual data on major salivary gland patients from 2008. Cases were matched by patient, time of diagnosis within a year, and cancer site. If diagnosis dates differed the earliest was taken. Blank or non-specific registry codes were updated if more specific information was available in the matched audit record.

The original intention was to augment the number of registered cases with any additional audit data. In fact only a small number of audit cases did not match the registry extract. Further cross-referencing with the registry showed most had a differing site or failed the inclusion criteria. The remainder were possibly late registrations in 2013 and/or complex cases where diagnosis may have taken longer to finalise. As this number was small and these cases had not been validated by the Office for National Statistics (ONS) they were excluded.

Initial analysis included all cases based on anatomical codes. Then histological codes were used to exclude types of cancers that do not arise primarily in the major salivary glands such as non-solid cancers of the lymph nodes or blood where site of origin is uncertain. See Appendix A for list and numbers of primary salivary cancer histological types and codes.

7075 primary salivary cases were analysed further. Data was grouped by age, sex, topography, histological type, deprivation and ethnicity. Direct age-standardised rates (DSRs) were calculated using the European Standard Population (ESP 2013) for five-year pooled periods, or ten-year pooled period where numbers were small. Histological codes were grouped into the most common types and an other category for all remaining tumours. Age-specific rates (ASRs) were calculated for broad age groups. Proportions of new cases by deprivation quintile and broad ethnic groups were also calculated.

Treatment information was combined from registry information and supplemented with information from audit treatment records. Relative survival was estimated using the method described by Estève et al[9] using the algorithm *strel* developed by Coleman et

al[10]. Relative survival estimates are adjusted to allow for deaths from causes other than cancer and are useful when disease-specific cause is not available. Observed survival is compared with the expected survival of an age- and sex-matched population, so gives a more accurate estimate of the impact of the disease than crude mortality rates.

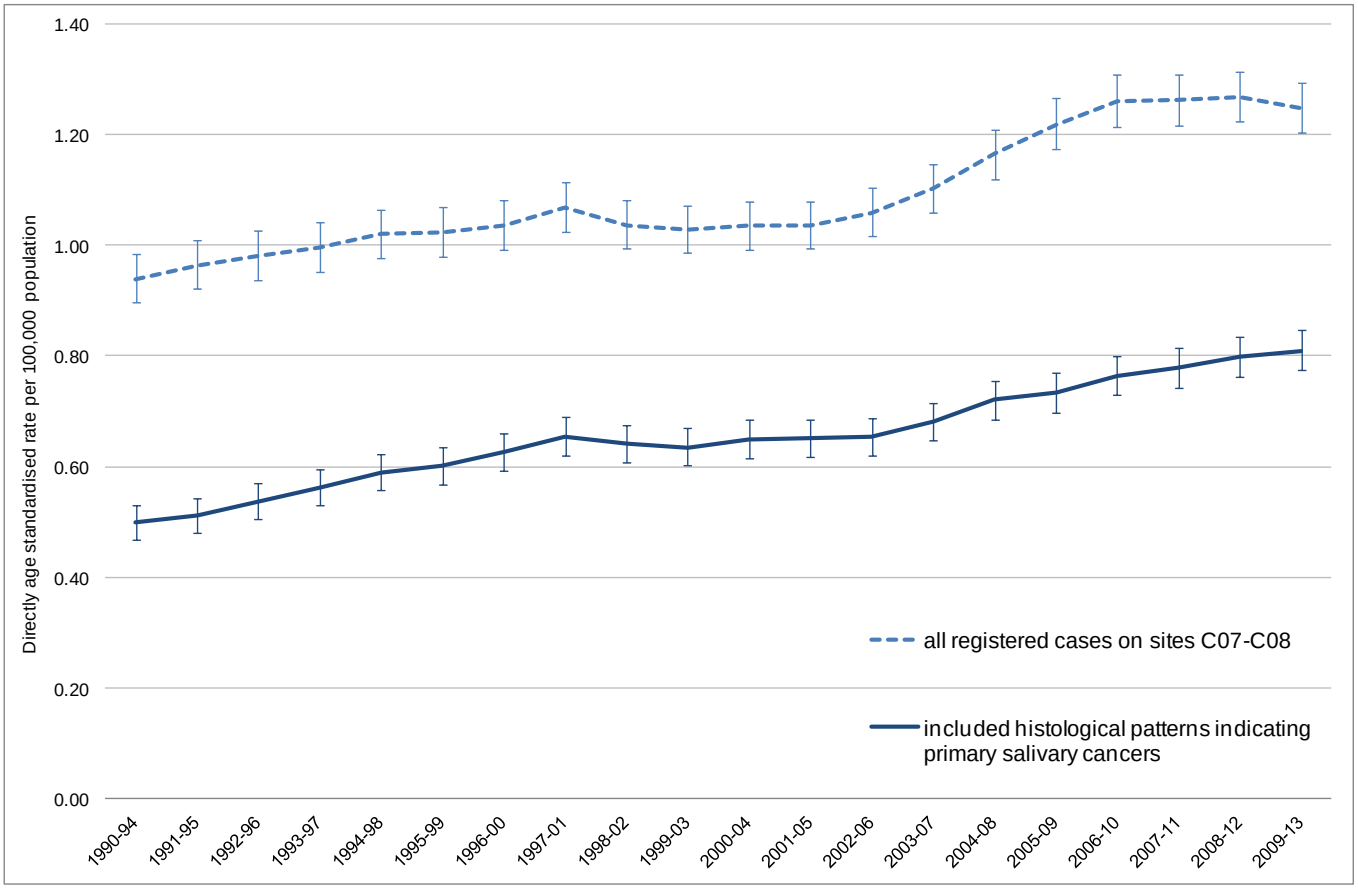
Results

Examination of histological classification

There has been a significant rise in new diagnoses of salivary gland cancer since 1990. Over the last decade there has been a sustained annual rise of 2.5%. Figure 1 (below) shows the incidence rate has risen from 0.94 cases per 100,000 of the population during 1990-94 up to 1.25 cases in 2009-13. Examination by histological group showed 1,972 cases (17%) were squamous cell carcinoma (SCC). SCC is the most common type of cancer in other head and neck sites but is an exceptionally rare type of primary salivary gland[11].

The high proportion of SCCs suggests the majority of these cases did not originate in the salivary glands and are invasive or metastatic cancers of other sites.
A further 2,116 cases (19%) do not have any detailed histological classification available in the registry and are recorded as non-specific tumours. A proportion of these are also thought to be SCCs.

Figure 1: direct age-standardised incidence rates for all major salivary gland cancers (C07 to C08) vs. included primary salivary gland cancers based on histological types, rolling five years 1990-94 to 2009-13



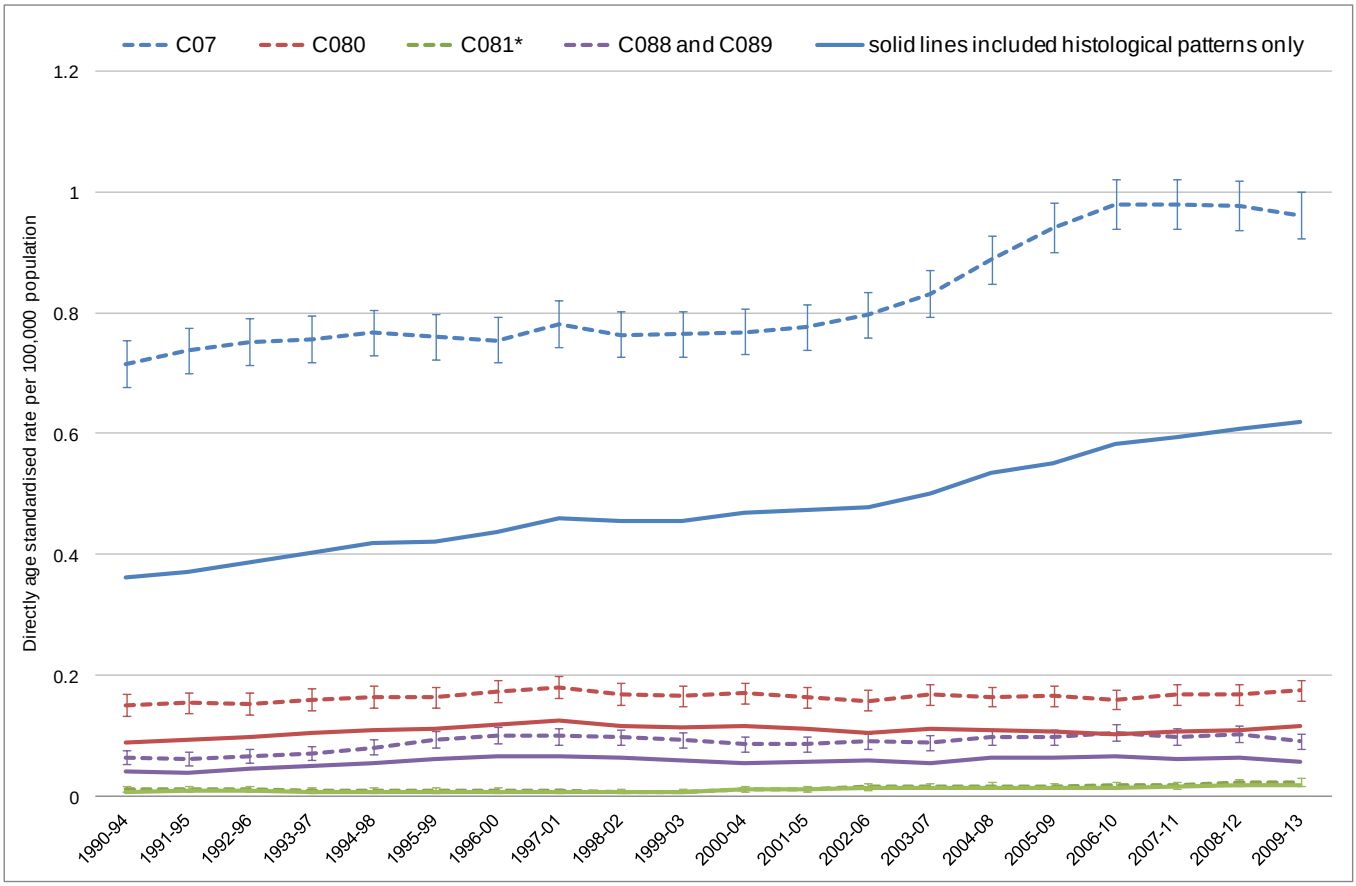
National statistics have been based on anatomical codes so the incidence rate of all registered salivary cases was compared to cases with confirmed histological diagnoses indicating a primary salivary cancer.

By selecting diagnoses based on site and morphological description, the incidence rate has reduced to 0.5 in 1990-94 and 0.81 in 2009-13 – see figure 1. Interestingly, the incidence rate trends have remained similar. Excluding cancers unlikely to have originated in the major salivary glands reduces the incidence rate of de novo primary salivary malignancies in the major glands by around 38%. For recent years this excludes about 200 cases per year. These are important to exclude as non-primary SCCs will have a different aetiology, course and worse prognosis. Notably the proportion of SCCs registered has remained stable over the period.

Figure 2 shows the impact of the exclusion across each major salivary gland site. For included histological types the incidence rate has reduced by 40% in the parotid (C07), 33% in the submandibular (C080), 21% in the sublingual (C081) and 38% in overlapping or unspecified glands combined (C088 and C089).

Slight reductions in incidence rates of all parotid cases and of overlapping sites in 2009-13 are not significant but there is a lower proportion of unspecific tumours recorded since 2010. This may be due to improved data quality and reflect richer information into the registry process from electronic pathology reporting. It will be interesting to monitor this in future to see if this trend continues.

Figure 2: direct age-standardised incidence rates for all cancers vs. included primary salivary histological types, rolling fiveyears 1990-94 to 2009-13, by site



The following analysis focuses on the selected salivary histological types to gain a clearer understanding of primary major salivary gland cancers and why incidence may be rising.

Anatomical site and sex

The most common site of newly diagnosed major salivary gland cancer is in the parotid glands. Over the period, the incidence rate of parotid gland cancers has risen significantly from 0.4 to 0.6 per 100,000 persons – see figure 2. Incidence of sublingual gland cancers has also risen significantly but five-year rates are based on small numbers so are not robust. Table 1 examines ten-year data and here the rise in sublingual and parotid cancers is significant across the two decades.

The numbers of cases in the submandibular and overlapping/unspecified sites have increased, yet there have been no significant rises in incidence rates. Consequently, the proportion of

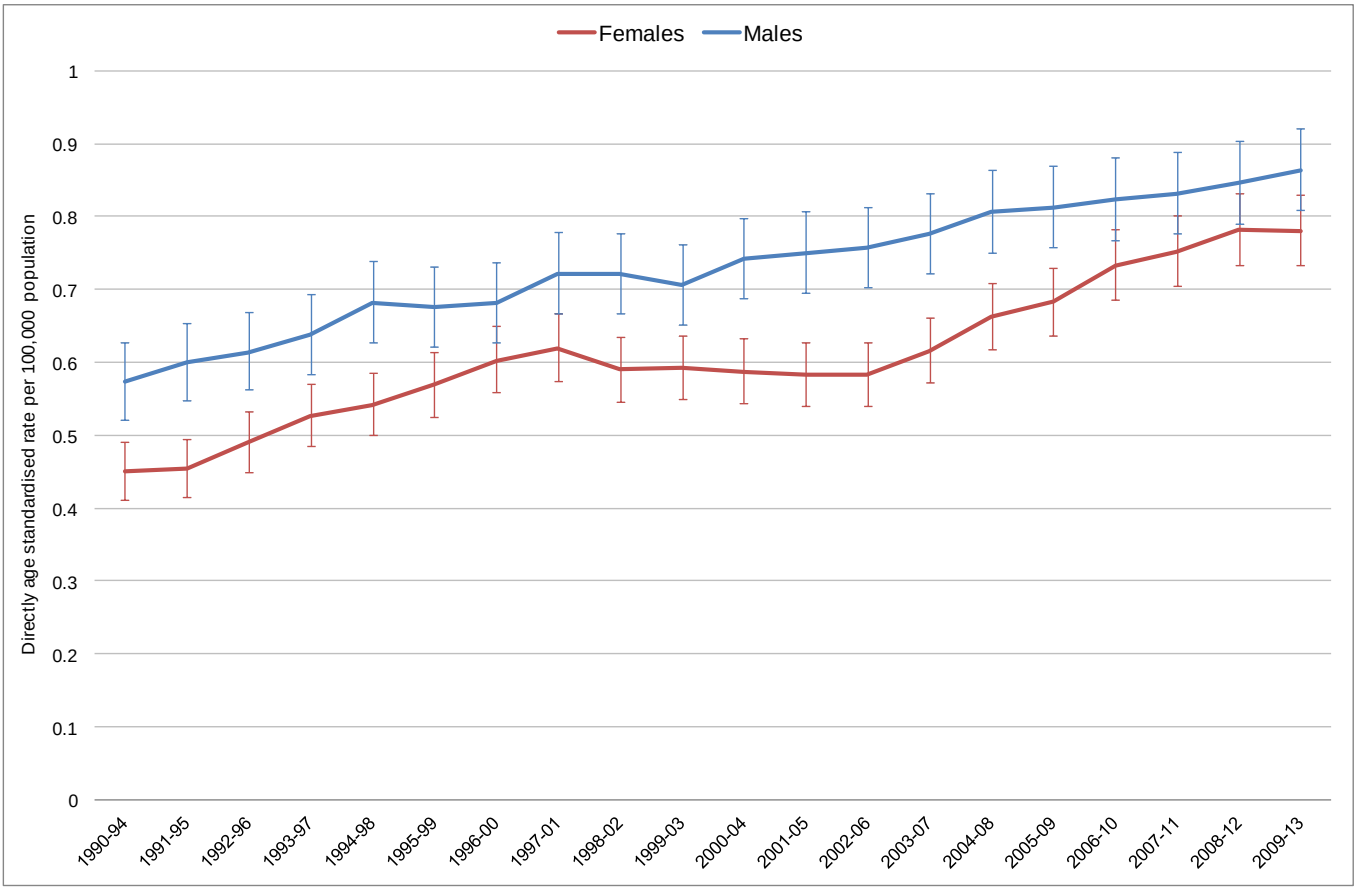
parotid gland cancers registered has increased over time so in 2009-13, 77% of cases were in the parotid, 14% in the submandibular, 2% in the sublingual glands and the remaining on overlapping or unspecified major salivary glands.

Table 1: numbers and directly age-standardised incidence rates (DSRs) with confidence intervals per 100,000, decades 1994-2003 and 2004-2013, by site and sex

Anatomical Site	Sex	1994-2003				2004-2013			
		number (n)	incidence rate (DSR)	lower CI (LCI)	upper CI (UCI)	number (n)	incidence rate (DSR)	lower CI (LCI)	upper CI (UCI)
Parotid C07	persons	1891	0.44	0.42	0.46	2754	0.58	0.56	0.60
	males	975	0.52	0.49	0.55	1413	0.66	0.62	0.69
	females	916	0.39	0.36	0.41	1341	0.53	0.50	0.56
Submandibular C080	persons	476	0.11	0.10	0.12	536	0.11	0.10	0.12
	males	221	0.12	0.10	0.13	258	0.12	0.10	0.13
	females	255	0.11	0.10	0.13	278	0.11	0.10	0.12
Sublingual C081	persons	30	0.01	0.00	0.01	77	0.02	0.01	0.02
	males	11	0.01	0.00	0.01	28	0.01	0.01	0.02
	females	19	0.01	0.00	0.01	49	0.02	0.01	0.03
Overlapping/ unspecified C088/9	persons	244	0.06	0.05	0.06	280	0.06	0.05	0.07
	males	101	0.05	0.04	0.07	118	0.05	0.04	0.06
	females	143	0.06	0.05	0.07	162	0.06	0.05	0.08
All sites	persons	2641	0.61	0.59	0.64	3647	0.77	0.74	0.79
	males	1308	0.69	0.66	0.73	1817	0.84	0.80	0.88
	females	1333	0.57	0.54	0.60	1830	0.72	0.69	0.76

Incidence in both males and females has risen significantly over the period for all major salivary gland cancers. Figure 3 (below) shows that incidence in males has historically been higher than in females but this gap has reduced and is not significant in the most recent period.

Figure 3: direct age-standardised incidence rates (DSRs) for major salivary gland cancers, rolling five-years 1990-94 to 2009-13, by sex



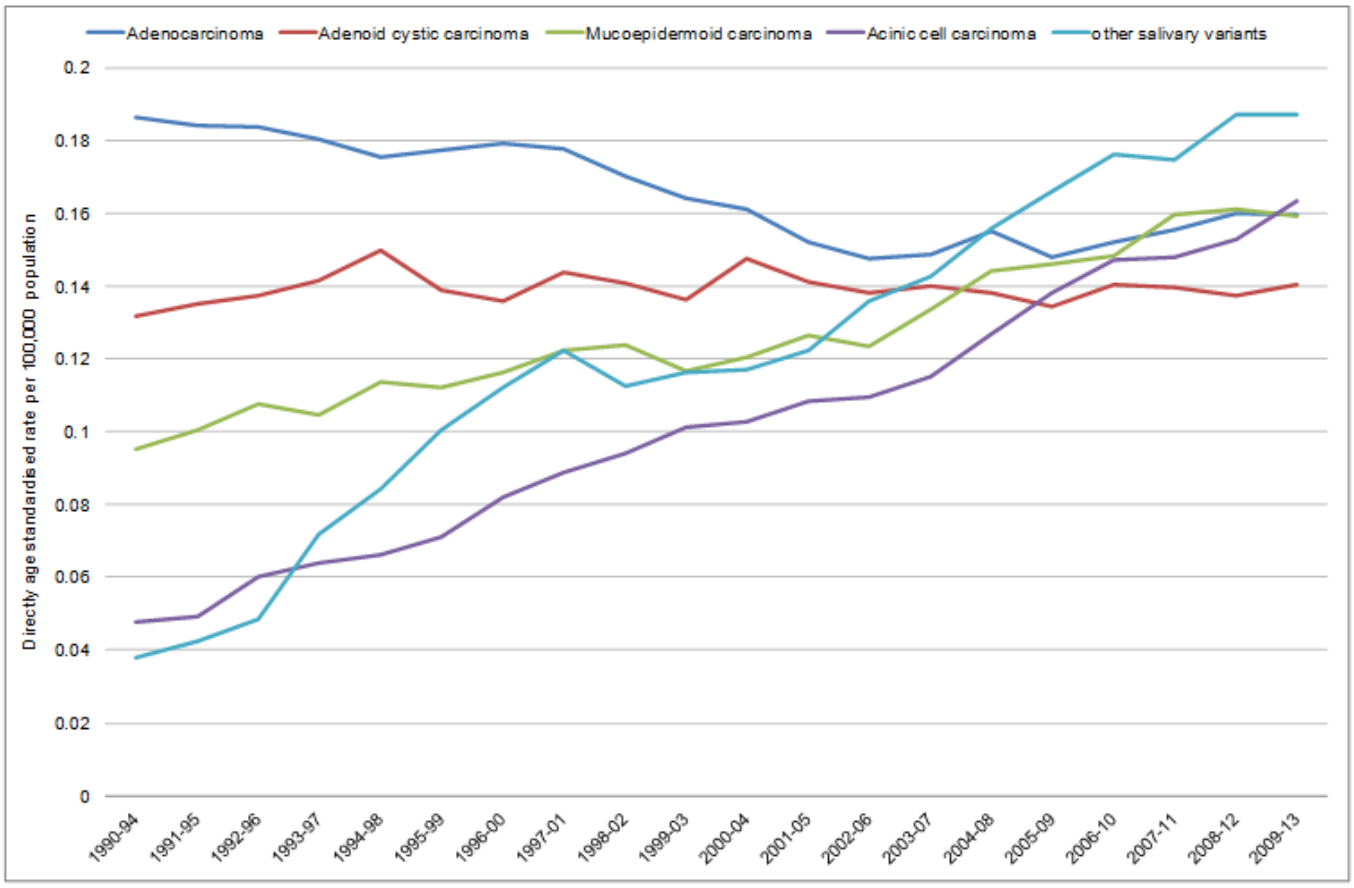
In other head and neck sites male incidence rates usually exceed females in a ratio of at least 2 to 1. Across major salivary gland sites there is a more varied picture of incidence between the sexes. Overall, an increase in the female incidence rate in the parotid gland has contributed most to the narrowing gap between the sexes over the last decade – see table 1. Examination by histological type shows again a mixed gender distribution in different salivary variants.

Histological type

Excluding squamous cell carcinomas, the four most common histological types combined comprise 77% of diagnoses between 2009-2013 in England. These are: adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma and acinic cell carcinoma. All remaining rarer salivary cancers were grouped into an ‘other’ group.

There have been significant increases in the incidence of acinic cell and mucoepidermoid carcinomas and in other types – see figure 4. The incidence rate of mucoepidermoid carcinomas has increased by 50%. The rate of acinic cell carcinomas has trebled and other types has quadrupled since 1991 to 2013.

Figure 4: direct age-standardised incidence rates (DSRs) across all sites, rolling five-years 1990-94 to 2009-13, by histological type



The incidence of adenoid cystic carcinoma has remained stable over the study period.

Diagnoses of unspecified adenocarcinoma declined during the 1990s suggesting changes in coding or diagnostics may have shifted some cases to other diagnoses. Adenocarcinoma NOS would be correctly used only for a very small proportion of salivary neoplasms that cannot be otherwise classified but is likely to have been used as a generic code to cover many potentially identifiable types, particularly some high grade types such as salivary duct carcinoma. The rate of registration of adenocarcinoma has levelled off in the latter decade while the incidence of rarer salivary variants has increased. Increasing awareness of the rarer types may also account for some of the increases in the earlier decade. Table 2 highlights how this has altered the relative frequencies of the main tumour types over time.

In the other group, two histological types account for nearly half of diagnoses: epithelial-myoepithelial cancer and carcinoma ex pleomorphic adenoma (Ca ex PA). The incidence of these appears to have risen rapidly, but annual numbers diagnosed in England are low, almost certainly reflecting miscoding, probably into the adenocarcinoma category as neither is particularly rare but both are prone to underdiagnosis. The remaining types occur more infrequently in numbers too small for analysis over time. Where numbers of others are very small, cases have been aggregated into low and high grade types – see table 2. There are

currently over 20 malignant salivary types described so their morphological diversity combined with their rarity makes histopathological diagnoses a challenge[11,12].

Table 2: numbers, percentages and directly age-standardised incidence rates (DSRs), 1994-03 to 2004-13, by histological group

Histological type	1994-2003					2004-2013				
	n	%	DSR	LCI	UCI	n	%	DSR	LCI	UCI
Adenocarcinoma	704	26.7	0.17	0.16	0.18	721	19.8	0.16	0.15	0.17
Adenoid cystic carcinoma	631	23.9	0.14	0.13	0.15	670	18.4	0.14	0.13	0.15
Mucoepidermoid carcinoma	510	19.3	0.12	0.11	0.13	746	20.5	0.15	0.14	0.16
Acinic cell carcinoma	373	14.1	0.08	0.08	0.09	715	19.6	0.15	0.13	0.16
Epithelial-myoepithelial	94	3.6	0.02	0.02	0.03	176	4.8	0.04	0.03	0.04
Carcinoma ex pleomorphic adenoma	78	3.0	0.02	0.01	0.02	174	4.8	0.04	0.03	0.04
Basal cell adenocarcinoma	43	1.6	0.01	0.01	0.01	89	2.4	0.02	0.02	0.02
Salivary duct carcinoma	25	0.9	0.01	0.00	0.01	68	1.9	0.01	0.01	0.02
Undifferentiated carcinoma	27	1.0	0.01	0.00	0.01	39	1.1	0.01	0.01	0.01
other high grade salivary variants	77	2.9	0.02	0.01	0.02	98	2.7	0.02	0.02	0.03
other low grade salivary variants	62	2.3	0.01	0.01	0.02	106	2.9	0.02	0.02	0.03
All types	2641	100	0.61	0.59	0.64	3647	100	0.77	0.74	0.79

NB rarer types of salivary variant not analysed as numbers small see appendix

The differing patterns of distribution by sex, median age and anatomical site in the main histological salivary types are shown in table 3.

Table 3: percentages by sex, site and median ages,1994-03 to 2004-13, by histological group

Histological type	1994-2003						2004-2013					
	% male	mdn age	% C07	% C080	% C081	% C088/9	% male	mdn age	% C07	% C080	% C081	% C088/9
Adenocarcinoma	60.6	68	67.9	11.2	0.3	10.3	61.7	68	70.0	10.3	0.9	9.4
Adenoid cystic carcinoma	35.0	55	41.6	36.8	2.1	9.7	44.0	58	40.7	35.6	6.0	8.8
Mucoepidermoid carcinoma	54.3	59	72.9	10.7	1.8	7.3	46.2	53	76.2	10.4	2.0	5.7
Acinic cell carcinoma	39.4	56	87.0	3.6	0.3	4.6	42.5	54	91.2	2.0	0.3	3.2
Epithelial-myoepithelial	44.7	69	74.8	7.8	0.0	8.7	47.2	67	77.1	9.6	0.5	6.4
Ca ex PA	47.4	61	52.7	15.1	2.2	16.1	46.6	64	72.0	14.5	0.5	6.5
Basal cell adenocarcinoma*	44.2	67	78.3	8.7	0.0	6.5	51.7	66	71.4	9.2	1.0	9.2
Salivary duct carcinoma*	68.0	69	80.8	11.5	0.0	3.8	67.6	66	64.5	11.8	2.6	10.5
Undifferentiated carcinoma*	74.1	66	88.9	11.1	0.0	0.0	64.1	78	80.5	9.8	0.0	4.9
other high grade variants	73.1	70	73.5	14.5	0.0	6.0	63.3	74	81.2	12.9	0.0	3.0
other low grade variants	62.9	67	68.2	17.6	0.0	7.1	60.4	67	61.2	6.7	1.7	15.2
All types	49.5	62	65.5	16.5	1.0	8.5	49.8	61	70.1	13.6	2.0	7.2

**Based on small numbers.C07=parotid, C080=submandibular, C081=sublingual, C088/9=overlapping and unspecified major salivary gland.*

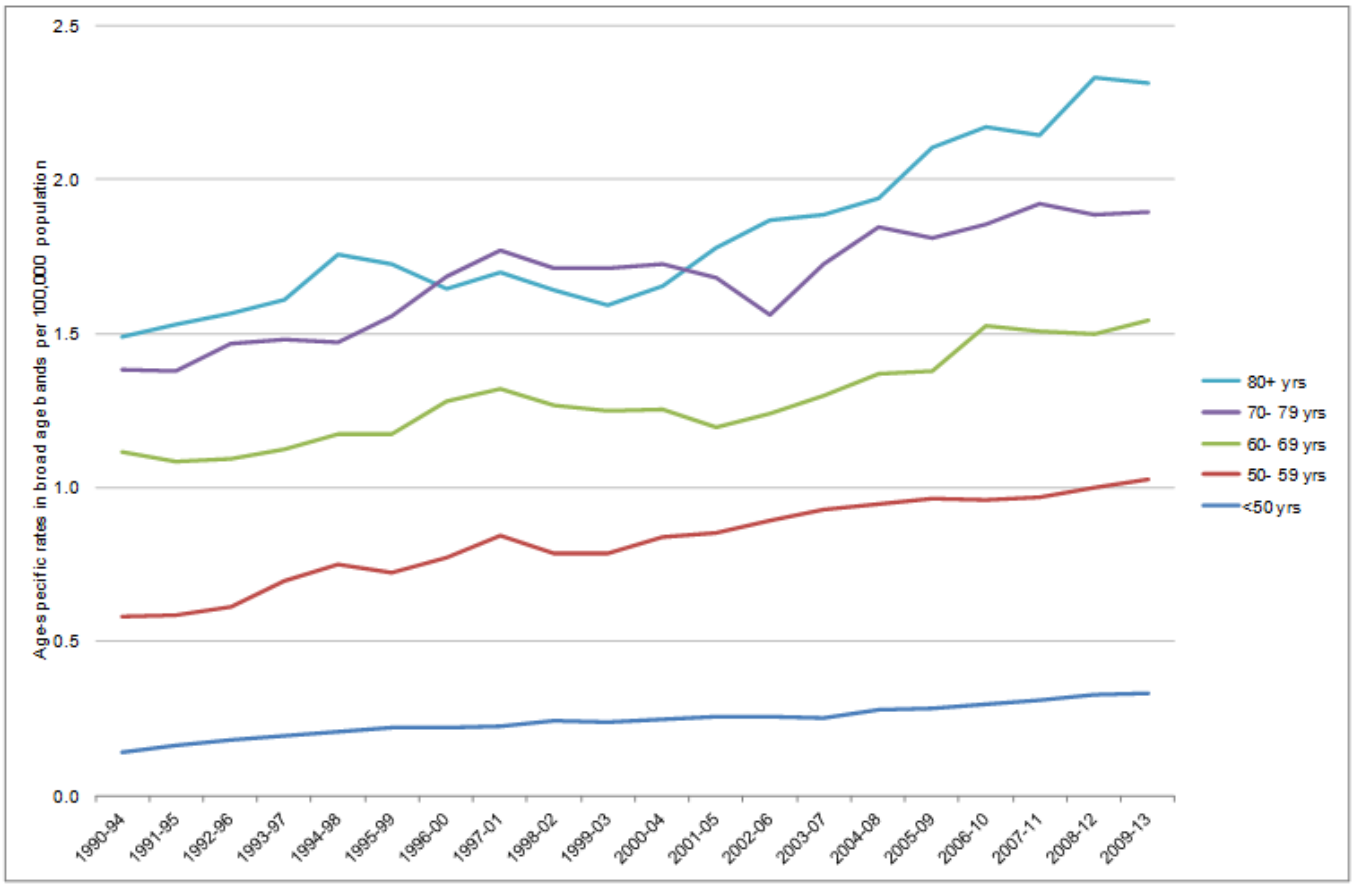
Although the median age for all salivary cancers has marginally reduced from 62 to 61 years the distribution by age is different in the various types. Table 3 shows three types: adenoid

cystic carcinoma, mucoepidermoid carcinoma and acinic cell carcinoma all have median age of incidence less than 60 years of age.

Age

There have been rises in all age-specific rates overtime – see figure 5. Incidence rates are highest in 70- to 79-year-olds and the over-80s. Throughout the period the median age at diagnosis has reduced from 65 years in 1990-94 and to 61 in 2009-13. Although there has been a steep rise in incidence in over 80 year olds, the numbers of cases in the eldest group account for about 14% of the total. Rates have risen most in the youngest two age bands. In 2009-13 nearly 30% of all cases were under 50 years, suggesting that earlier age of diagnosis is contributing to the increase in incidence. This may be largely due to the younger age profile of mucoepidermoid and acinic cell carcinoma patients as seen in table 3.

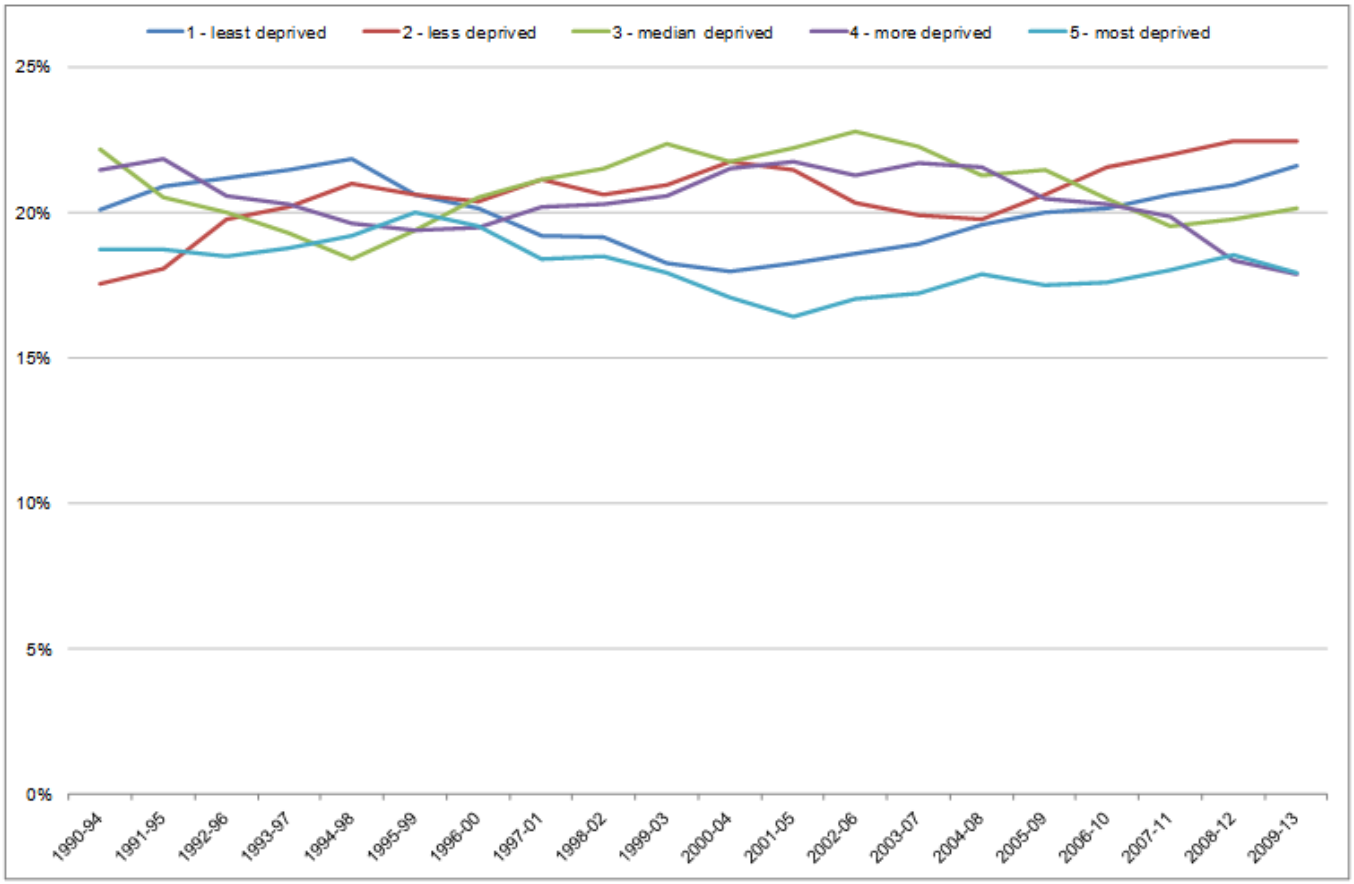
Figure 5: age specific incidence rates (ASRs) for all sites and all persons by broad age groups, 1990-94 to 2007-13



Deprivation

Figure 6 shows trends in the percentages of cases registered by income deprivation of postcode at diagnosis (Index of Multiple Deprivation). Overall trends are not significant. This pattern is different to that observed in some other main head and neck sites (particularly larynx, oral cavity and oropharynx) where incidence is positively correlated with rising deprivation.

Figure 6: percentage of new cases by income deprivation quintile, 1990-94 to 2009-13

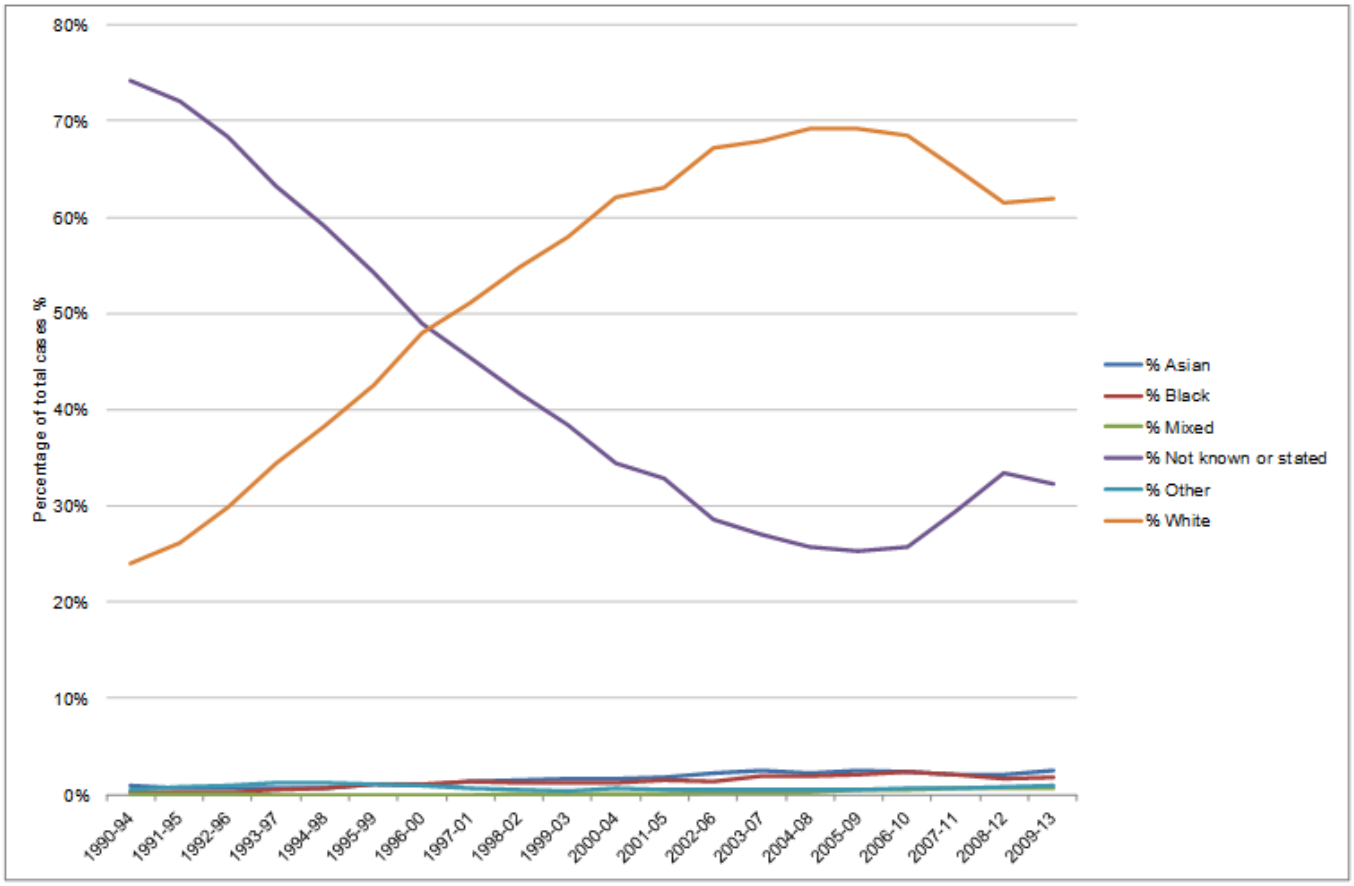


Ethnicity

Figure 7 highlights issues of data capture and recording of ethnic group. Since the beginning of the period there has been improvement in the completeness of recording of ethnic group up to the late 2000s. During this later period there have been significant organisational changes to the NHS – Public Health England and regional cancer registries migrated into a single national registry. Over this time there was some loss in completeness, but it is important for epidemiological analysis that this is restored and recording of ethnicity continues to improve.

The frequency of mucoepidermoid cases observed was higher in the general non-white population, 39% compared with 19% but the numbers are too small to examine reliable incidence rates by detailed ethnic group.

Figure 7: percentage of new cases by ethnic groups, 1990-94 to 2009-13



Completeness of staging and grading variables

Staging and grading information has been collected historically but has only been comprehensively captured on registry and audit records recently. Completeness of registry stage fields has improved rapidly from 2011. The audit holds more data, but as collection of salivary gland cases began from 2008 only the most recent years have a usable quantity of stage and grade information. In 2013, GX grade not assessed, was 44% and blank or unknown was 13%.

Staging data was slightly better recorded in 2013 as 66% of cases had a valid stage. This means analysis by stage and grade is limited. However, even in 2013, a third of salivary cases are still unstaged which contrasts with other head and neck sites where about 15% of cases were unstageable or unknown in the audit's 10th report. Due to the complexity of diagnosing major salivary gland cancer it may be this affects data capture. Where cases are staged, they are almost equally split into early (stage 1 and 2) and late

(stage 3 and above) diagnoses. More information is necessary to examine histological types by stage.

Treatments

There were 7,075 cases examined for treatment information in registry+audit treatment records. Cases with death certificate only and with invalid or unlinked NHS numbers were excluded – 5,969 cases had one or more treatment records linked, 16% had no recorded treatment. Where cases had a record, 89 had treatment type and/or treatment date missing or 'unknown'. This leaves a cohort of 5,880 major salivary gland cases with over 11,000 treatments as a resource for further research. Ninety per cent had a first treatment of surgery, 11% had radiotherapy or chemoradiotherapy first, and 2% had chemotherapy as an initial treatment. Treatment intent is well recorded in the recent audit data but was not so complete historically. Intent is not directly captured on the registry so it was not possible to discriminate palliative from curative treatments for the earlier cases.

Table 5: combined treatment cohorts (ordered) by site, numbers and percentages

Treatment cohort (in order)	Parotid C07		Submandibular C080		Sublingual C081		Overlapping / unspec C088/9		All sites	
	n	%	n	%	n	%	n	%	n	%
S+R	2031	45.4	440	45.3	34	32.7	115	27.1	2620	43.9
S	1767	39.5	356	36.7	55	52.9	225	52.9	2403	40.3
R	389	8.7	99	10.2	8	7.7	53	12.5	549	9.2
Treatment NK	60	1.3	19	2.0			10	2.4	89	1.5
S+C+R or S+ChR	76	1.7	22	2.3	4	3.8	3	0.7	105	1.8
S+C	25	0.6	13	1.3	1	1.0	3	0.7	42	0.7
C+R or ChR	27	0.6	9	0.9			6	1.4	42	0.7
R+S	31	0.7	3	0.3			3	0.7	37	0.6
C	22	0.5	3	0.3			4	0.9	29	0.5
R+C	18	0.4	6	0.6			2	0.5	26	0.4
other cohort	23	0.5	1	0.1	2	1.9	1	0.2	27	0.5
Total treated	4469	100	971	100	104	100	425	100	5969	100
No treatment	747	14.3	176	15.3	16	13.3	167	28.2	1106	15.6
Total cases	5216	100	1147	100	120	100	592	100	7075	100

S=surgery, R=radiotherapy, C=chemotherapy, ChR=chemoradiotherapy

Most treated cases have surgery with or without adjuvant radiotherapy. Forty per cent had surgery, 44% had surgery with radiotherapy and 9% had radiotherapy as a single modality treatment. Where the site code was overlapping or unspecified (C088/9) there was a higher proportion of cases where no treatment was given suggesting these may be more advanced cases. The percentage of cases with no treatment recorded in the

most recent time period is 10% (2009 to 2013) compared with 15.6% for the whole period. Table 6 highlights under-recording of treatment data historically.

Table 6: treatment cohorts by stage, numbers and percentages

Treatment cohort (in order)	Stage 1		Stage 2		Stage 3		Stage 4		Not staged*		All cases	
	n	%	n	%	n	%	n	%	n	%	n	%
S+R	109	36.9	135	50.6	98	58.0	190	57.4	2088	42.6	2620	43.9
S	174	59.0	113	42.3	50	29.6	45	13.6	2021	41.2	2403	40.3
R	5	1.7	11	4.1	14	8.3	44	13.3	475	9.7	549	9.2
Treatment NK	3	1.0	5	1.9	1	0.6	10	3.0	70	1.4	89	1.5
S+C+R or S+ChR	1	0.3	3	1.1	3	1.8	13	3.9	85	1.7	105	1.8
S+C					1	0.6	3	0.9	38	0.8	42	0.7
C+R or ChR					1	0.6	9	2.7	32	0.7	42	0.7
R+S							2	0.6	35	0.7	37	0.6
C							4	1.2	25	0.5	29	0.5
R+C	1	0.3					2	0.6	23	0.5	26	0.4
other cohort	2	0.7			1	0.6	9	2.7	15	0.3	27	0.5
Total treated	295	100	267	100	169	100	331	100	4907	100	5969	100
No treatment	9	3.0	5	1.8	5	2.9	14	4.1	1073	17.9	1106	15.6
Total cases	304	100	272	100	174	100	345	100	5980	100	7075	100

**includes unstageable tumours plus tumours where stage not known or blank*

The use of surgery as a single treatment is negatively associated with advancing stage; nearly 60% of the earliest, stage 1 cases have surgery alone. Radiotherapy use, as a single modality or in combination post-surgery, increases with disease advancement. Unlike other head and neck cancers, chemoradiotherapy alone or with surgery is not widely used but where used this is largely for more advanced major salivary gland cancers.

Table 7: treatments by main histological types and others, numbers and percentages

Treatment cohort (in order)	Adenocarcinoma NOS		Adenoid cystic carcinoma		Mucoepidermoid carcinoma		Acinic cell carcinoma		Other salivary variant	
	n	%	n	%	n	%	n	%	n	%
S+R	613	58.9	653	62.7	489	47.0	406	39.0	459	44.1
S	397	38.1	408	39.2	585	56.2	559	53.7	454	43.6
R	213	20.5	123	11.8	77	7.4	41	3.9	95	9.1
Treatment NK	22	2.1	18	1.7	14	1.3	16	1.5	19	1.8
S+C+R or S+ChR	33	3.2	20	1.9	15	1.4	10	1.0	27	2.6
S+C	13	1.2	6	0.6	9	0.9	2	0.2	12	1.2
C+R or ChR	18	1.7	8	0.8	3	0.3	1	0.1	12	1.2
R+S	9	0.9	9	0.9	10	1.0	3	0.3	6	0.6
C	14	1.3	5	0.5	4	0.4	1	0.1	5	0.5
R+C	13	1.2	6	0.6	4	0.4			3	0.3
other cohort	13	1.2	4	0.4	2	0.2	2	0.2	6	0.6

Total treated	1358	100	1260	100	1212	100	1041	100	1098	100
No treatment	360	21.0	248	16.4	194	13.8	123	10.6	181	14.2
Total cases	1718	100	1508	100	1406	100	1164	100	1279	100

S=surgery, R=radiotherapy, C=chemotherapy, ChR=chemoradiotherapy

Survival data

Survival from major salivary gland cancer overall is good compared to other head and neck cancers with 91% of all cases in the total cohort surviving one-year after diagnosis, 80% after three years and 70% surviving 10 years after diagnosis. Over the two decades examined, no significant improvement in one-year survival was observed. There was a slight improvement in two, three, four and five-year survival for patients diagnosed in the most recent decade – see figure 8 and table 8.

Figure 8: estimated relative survival rates (RS%) of all persons from diagnosis by decade of diagnosis, 1994-2003 vs. 2004-2013

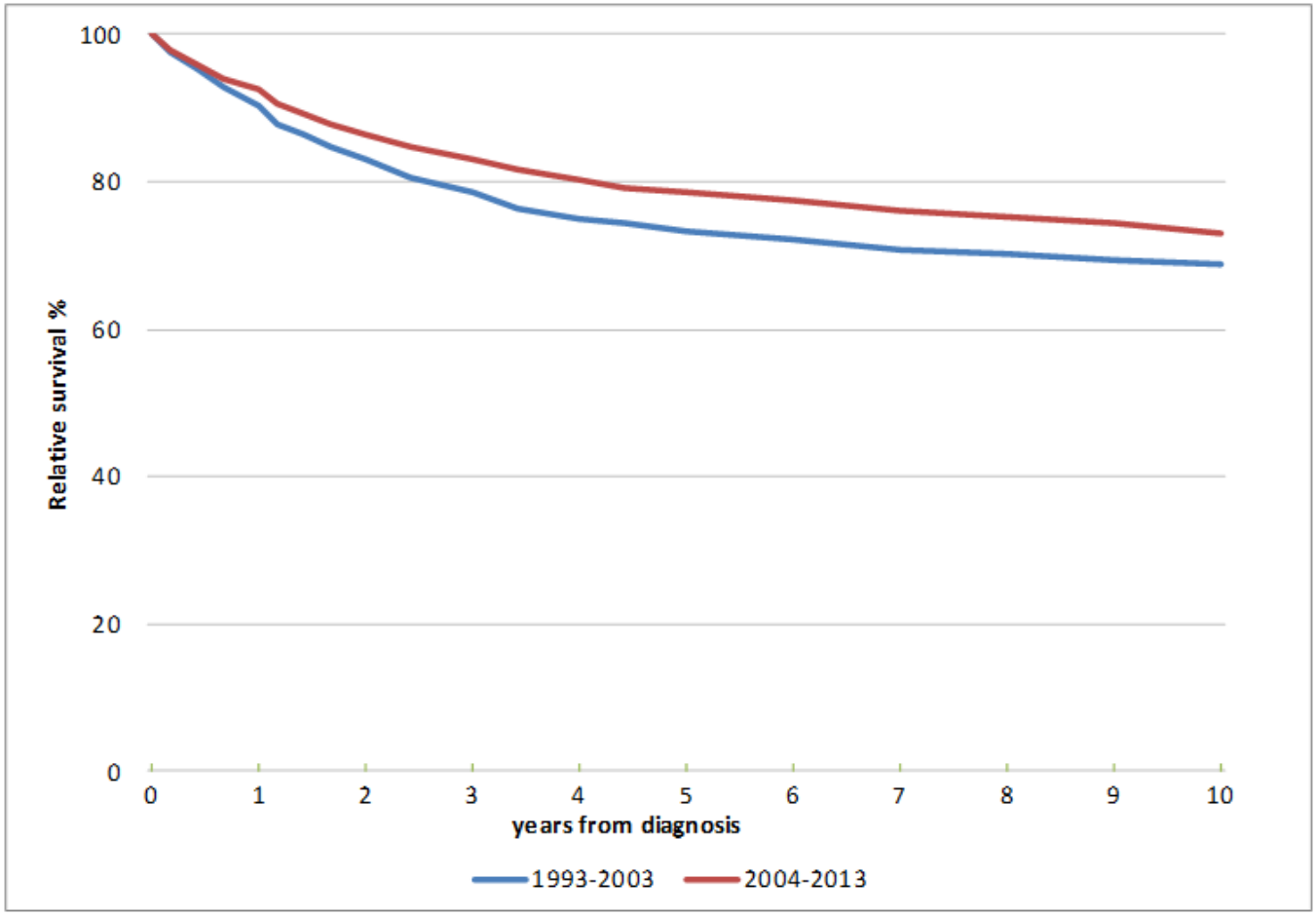


Table 8: estimated relative survival rates (RS%) in years from diagnosis by decade, 1994-2003 vs. 2004-2013 with confidence intervals

Survival time from diagnosis	Date of diagnosis 1994-2003			Date of diagnosis 2004-2013		
	RS%	LCI	UCI	RS%	LCI	UCI
1 year	90.4	89.0	91.6	92.6	91.5	93.5
2 years	83.0	81.2	84.6	86.4	85.0	87.7
3 years	78.5	76.5	80.3	83.1	81.5	84.6
4 years	75.0	72.9	76.9	80.2	78.4	81.8
5 years	73.4	71.2	75.4	78.7	76.9	80.5
10 years	68.8	66.4	71.1	73.0	69.9	75.8

Overall survival of females is significantly higher than males at all annual points examined up to 10 years. The gap in survival widens considerably in the first three years following diagnosis. For salivary gland cancer, this reflects the different gender patterns and prognoses of the various underlying histological types – see figure 9 and table 9.

Figure 9: estimated relative survival rates (RS%) in years from diagnosis by gender

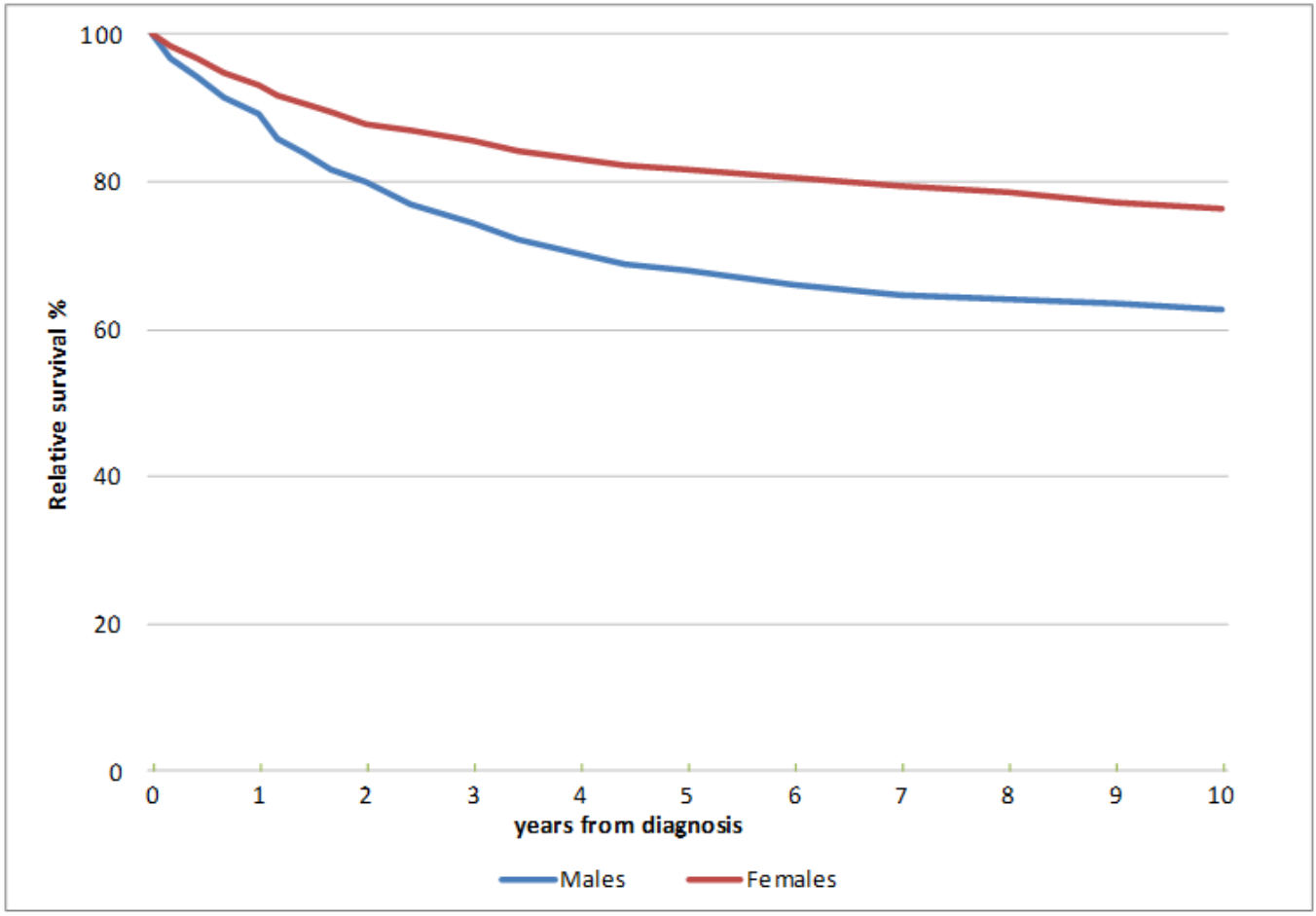


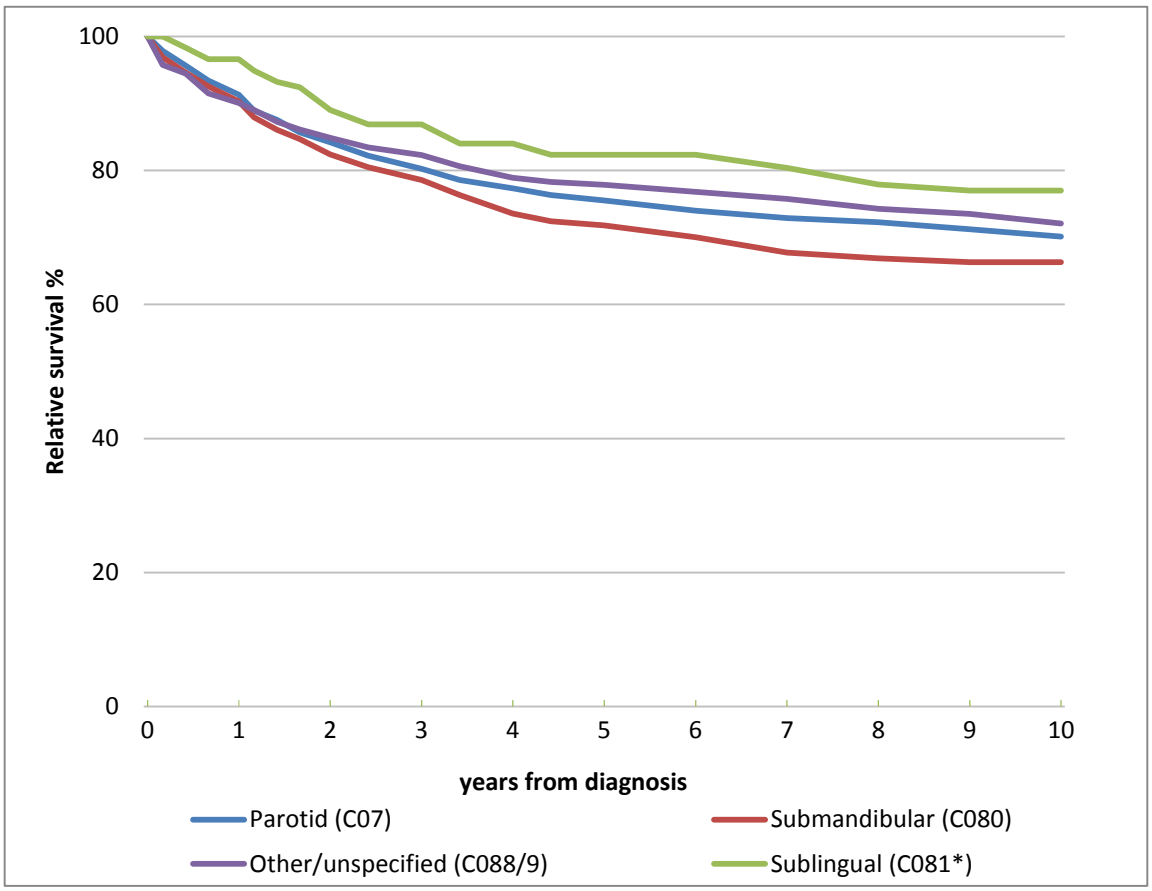
Table 9: estimated relative survival rates (RS%) in years from diagnosis by gender, all cases

Survival time	Males			Females		
	RS%	LCI	UCI	RS%	LCI	UCI
1 year	89.2	87.9	90.4	93.0	91.9	93.9
2 years	79.9	78.2	81.4	87.9	86.6	89.1
3 years	74.3	72.5	76.0	85.7	84.2	87.0
4 years	70.2	68.3	72.1	83.1	81.4	84.6
5 years	68.0	66.0	70.0	81.7	80.0	83.3
10 years	62.6	60.2	65.0	76.4	74.3	78.4

Table 10: estimated relative survival rates (RS%) in years from diagnosis by anatomical site of cancer diagnosis

survival time	Parotid C07			Submandibular C080			Sublingual C081*			Overlapping/ unspecified C088/9		
	RS%	LCI	UCI	RS%	LCI	UCI	RS%	LCI	UCI	RS%	LCI	UCI
1 year	91.3	90.4	92.2	90.3	88.1	92.1	96.6	89.4	98.9	90.1	86.9	92.5
2 years	84.2	83.0	85.4	82.4	79.6	84.8	89.0	80.8	93.9	84.9	81.0	88.0
3 years	80.2	78.9	81.5	78.6	75.6	81.3	86.8	78.1	92.2	82.3	78.0	85.8
4 years	77.3	75.8	78.7	73.6	70.3	76.6	84.0	73.5	90.6	78.9	74.4	82.8
5 years	75.5	74.0	77.0	71.8	68.4	75.0	82.3	71.0	89.6	77.8	73.1	81.9
10 years	70.1	68.2	72.0	66.3	62.3	70.0	77.0	59.7	87.6	72.1	66.1	77.2

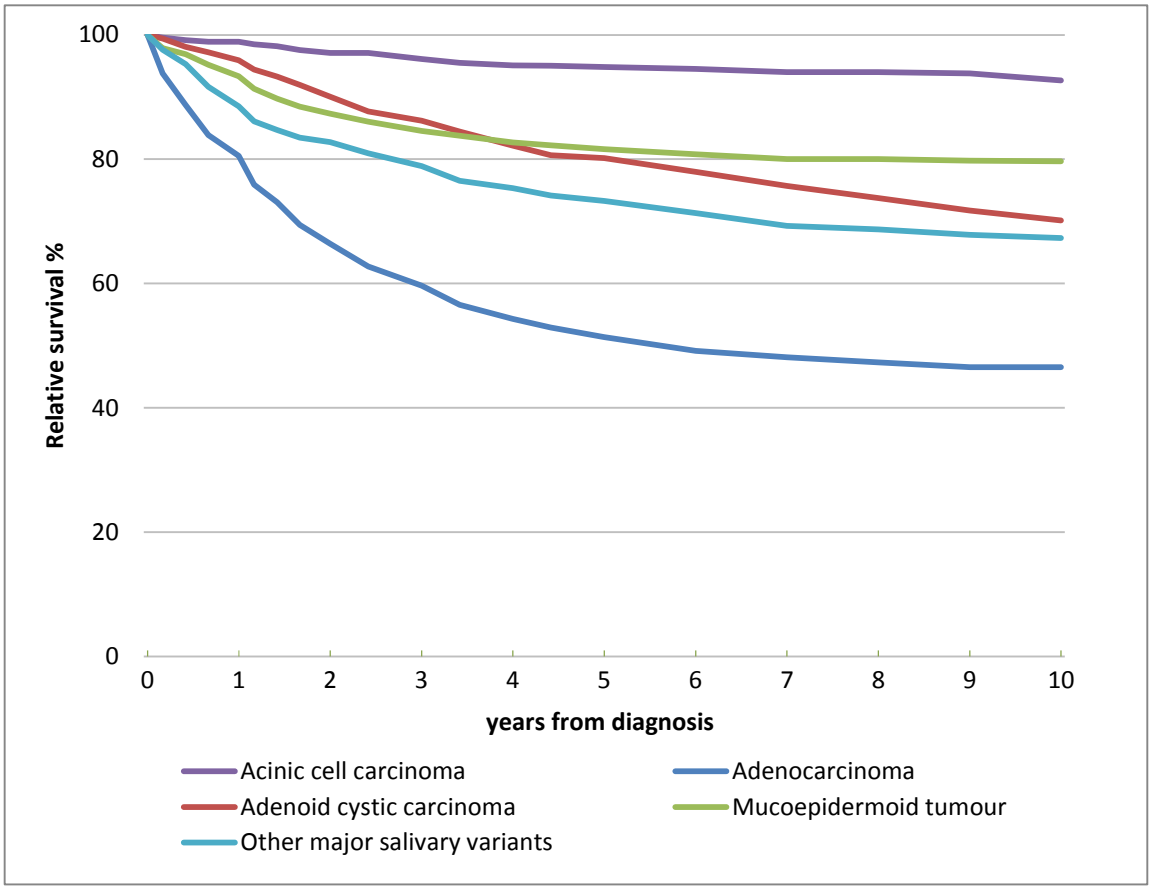
Figure 10: estimated relative survival rates (RS%) all cases by anatomical site



**rate based on small numbers*

Table 10 and figure 10 show no significant difference in survival estimates between sites. Although the relative survival rate over the first few years from diagnosis for sublingual gland (C081) appears higher, the numbers of cases are small so rates are not statistically robust.

Figure 11: estimated relative survival rates (RS%), all cases by main histological groupings



Acinic cell carcinoma has a significantly better prognosis than other salivary types with survival after ten years at 92%. Adenoid cystic carcinoma shows slower and more protracted disease development. Initial survival is good compared with other types but long-term follow-up of cases is important as disease progression is indicated ten years after diagnosis – see figure 11.

Table 11: estimated relative survival rates (RS%) in years from diagnosis by main histological types

survival time	Adenocarcinoma			Adenoid cystic carcinoma			Mucoepidermoid tumour			Acinic cell carcinoma			Other major salivary variants		
	RS%	LCI	UCI	RS%	LCI	UCI	RS%	LCI	UCI	RS%	LCI	UCI	RS%	LCI	UCI
1 year	80.6	78.4	82.5	95.9	94.6	96.9	93.3	91.5	94.8	98.9	97.6	99.5	88.5	86.3	90.4
2 years	66.4	63.8	68.8	90.0	88.1	91.7	87.3	85.0	89.4	97.1	95.4	98.2	82.7	80.1	85.1
3 years	59.6	56.9	62.3	86.2	84.0	88.1	84.6	81.9	86.8	96.1	94.1	97.4	78.9	76.0	81.5
4 years	54.3	51.5	57.1	82.2	79.7	84.4	82.7	79.9	85.2	95.1	92.8	96.7	75.3	72.1	78.2
5 years	51.4	48.4	54.3	80.2	77.5	82.6	81.6	78.7	84.2	94.9	92.3	96.6	73.3	69.9	76.4
10 years	46.6	43.3	49.8	70.2	66.7	73.3	79.7	76.1	82.8	92.7	89.0	95.1	67.3	62.9	71.3

Adenocarcinoma has a significantly worse prognosis than all other salivary types – observational studies describe this as varying between a low to high-stage tumour, but the poor prognosis seen here is probably accounted for by inclusion of high grade and relatively common entities such as carcinoma ex pleomorphic adenoma and salivary duct carcinoma that may have been either underdiagnosed or coded unspecifically.

Mucoepidermoid and the other group contain tumours of variable degrees of aggressiveness. The amount of staging information has not been sufficient to enable further analysis by type and stage but individual prognosis is largely thought to be dependent on this[12].

Table 12 and figure 12 show prognosis by stage for all cases in the cohort. As stated, staging data has been added from audit where the collection has been improving, yet the historic numbers staged are small so it is not possible to follow up adequate numbers of patients for the full period possible. Staging classification detail has also been collapsed into a general early and late stage.

Table 12: estimated relative survival rates (RS%) by overall TNM staging classification grouped into early and late stage

survival time	Early (Stage 1 or 2)			Late (Stage 3 or 4)			Stage blank, unknown or unstageable		
	RS%	LCI	UCI	RS%	LCI	UCI	RS%	LCI	UCI
1 year	99.9	-	-	93.9	91.0	95.9	96.2	95.5	96.7
2 years	99.5	95.2	99.9	77.1	72.7	80.9	87.8	86.7	88.8
3 years	99.2	95.1	99.9	67.9	62.8	72.4	82.4	81.2	83.6
4 years	98.6	93.9	99.7	61.1	55.3	66.4	78.8	77.5	80.1
5 years	97.9	92.3	99.5	53.7	44.4	58.0	76.2	74.8	77.6
10 years	-	-	-	-	-	-	70.7	69.0	72.3

As observed with other head and neck cancer sites, stage is a highly significant predictor of survival outcome. Comprehensive recording of the degree of advancement of tumours is important to fully understand the survival differences of individual tumours by detailed stage.

Figure 12: relative survival estimates by early (stages 1 and 2), late (stages 3 and 4) and unknown stage, all cases

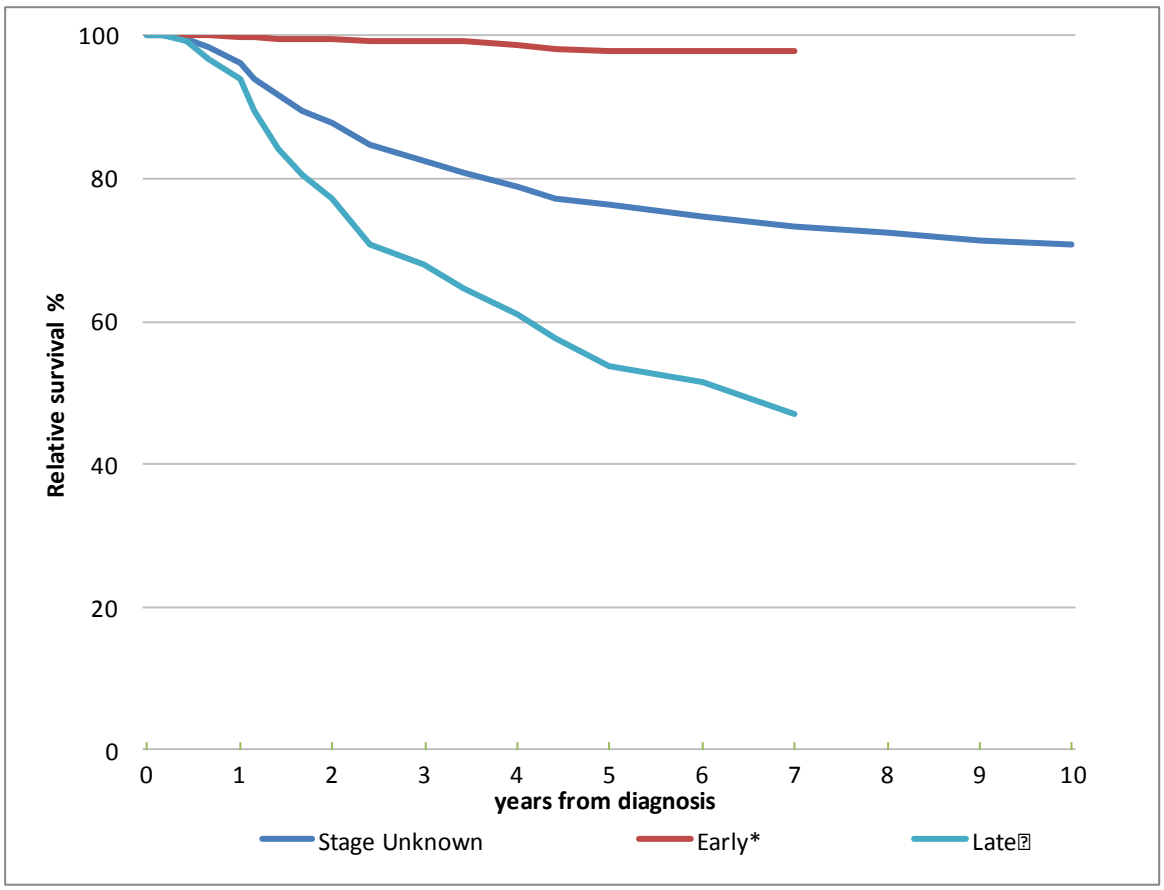
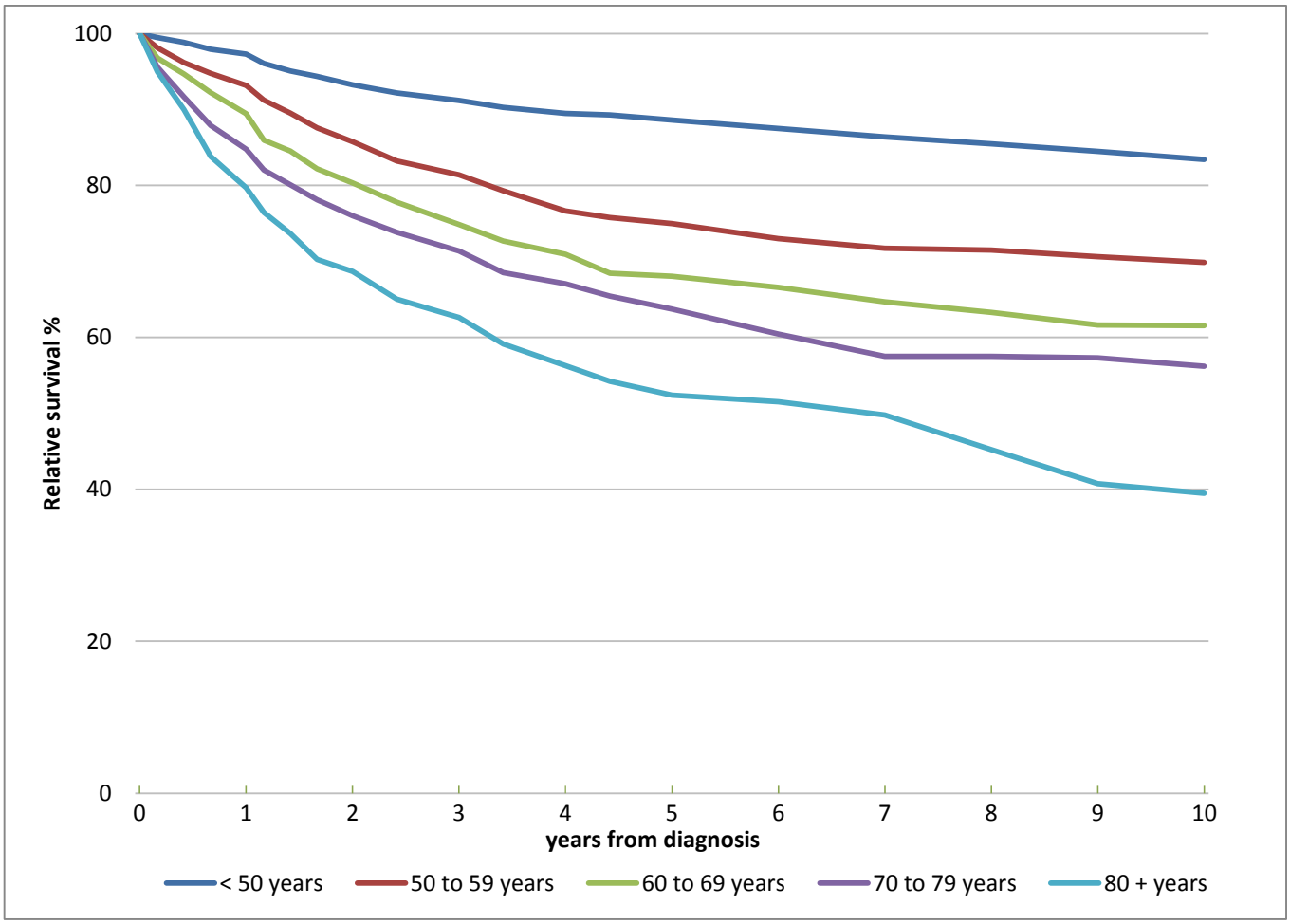


Table 13 and figure 13 show how outcome varies by broad age groups. In general prognosis decreases with increasing age.

Table 13: estimated relative survival rates (RS%) by broad age groups

survival time	< 50 years			50 to 59 years			60 to 69 years			70 to 79 years			80 + years		
	RS%	LCI	UCI	RS%	LCI	UCI	RS%	LCI	UCI	RS%	LCI	UCI	RS%	LCI	UCI
1 year	97.3	96.4	98.0	93.2	91.5	94.5	89.4	87.6	91.0	84.8	82.5	86.8	79.7	76.2	82.7
2 years	93.3	92.0	94.4	85.7	83.5	87.7	80.3	78.0	82.4	76.0	73.3	78.5	68.7	64.5	72.5
3 years	91.2	89.7	92.5	81.4	78.9	83.7	74.9	72.3	77.2	71.4	68.4	74.2	62.6	57.8	67.0
4 years	89.5	87.9	90.9	76.7	73.9	79.2	70.9	68.2	73.5	67.1	63.7	70.1	56.3	50.9	61.3
5 years	88.6	86.9	90.1	75.0	72.1	77.6	68.1	65.1	70.8	63.8	60.2	67.1	52.4	46.5	58.0
10 years	83.4	81.2	85.4	69.9	66.4	73.1	61.6	57.8	65.2	56.2	50.9	61.2	39.5	29.2	49.6

Figure 13 estimated relative survival rates (RS%) all cases by broad age bands



Conclusions

Major salivary gland cancer is a rare cancer but incidence are significantly increasing in England by 2.5% annually. Ascertaining why is challenging and complicated as the salivary glands often contain cancers that do not originate in the salivary glands. It is recommended that primary salivary squamous cell carcinomas are defined by exclusion of other metastatic cancers.

Rising incidence over time is observed across all ages and in both males and females. Most of the increase has been in cancers of the parotid gland. Analysis by histological type is key to understanding salivary gland cancers due to the number and differing behaviours of these diseases.

Four registration categories account for the majority of cases: adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma and acinic cell carcinoma but many other variants are recorded across the major glands. Significant and sustained increases in acinic cell and mucoepidermoid carcinomas and other rarer variants are observed. Classification of the main malignancies was prior to the period and expanded in 1992 so increasing awareness of rarer and newly described types in the early decade may have caused a shift away from coding of unspecific adenocarcinoma to the rarer other types. But mucoepidermoid and acinic cell carcinomas are well-established entities. The frequency of acinic cell and mucoepidermoid carcinomas has gone up to around 20% of malignancies which is now similar to frequencies observed in other countries.

Why these may have been previously under-recorded in England is not clear. A reduction in age profile could point to a younger age at diagnosis although there have been continued rises in all older age groups at the same time. Declining mortality from other causes such as CVD, stroke, COPD, lung and breast cancer[14] may explain the increase cancer in older ages. Gender and age appear to be interacting particularly in the mucoepidermoid carcinomas so hormones may have a role in addition to other gender differences in risk exposures[6].

Risk factors for major salivary gland are not well understood but ionising radiation is the most well established[15,16]. Occupational risks also suggested include rubber and car manufacturing, woodworking, metal working, and the beauty industry[8,13]. The risk factors of tobacco (smoking or chewing) and heavy alcohol use associated with other head and neck sites are not associated with major salivary gland cancers.

Surgery is the mainstay of treatment for major salivary gland cancer and 40% of cases have surgery alone as treatment. Surgery with post-operative radiotherapy is given to 44% of patients where tumours are more advanced or are thought to have the potential to spread. Unlike treatments for other head and neck sites, complex multi-modality

treatments such as chemoradiotherapy are not so widely used. The head and neck audit contains further treatment and care data items that can be investigated for patients from 2008 onwards.

Survival after primary salivary malignant neoplasms is generally better than published survival based on anatomical codes due to the exclusion of secondary salivary SCCs. Compared with other head and neck sites overall, survival of patients is good with over 70% alive ten years after diagnosis. Survival is strongly associated with stage so recognition of symptoms and early diagnosis is important. Prognosis also depends on the histological type with some, such as adenoid cystic carcinoma, showing a slow growth pattern and propensity for recurrence. Long-term monitoring of up to 10 years or more may be advised for patients with these types.

This report highlights the complexity and range of different diseases that form salivary gland cancer. It also underlines differences between cancers of the salivary glands and those of other head and neck sites. Going forward, increased accuracy in the recording of stage, grade, ethnic and histological detail is necessary for further reporting. In future it would be useful to report on minor salivary gland cancers to get a fuller understanding and investigate whether incidence rises are also occurring across the minor sites. This highlights the use of population-based cancer registry and audit datasets and establishes a detailed historic cohort that can be used as a resource for further research about major salivary gland cancers.

References

1 ONS Cancer Registration Statistics, England, 2013.

2 Profile of head and neck cancers in England: incidence, mortality and survival, 2011. http://www.ncin.org.uk/cancer_type_and_topic_specific_work/cancer_type_specific_work/head_and_neck_cancers/head_and_neck_cancer_hub/resources

3 Audit of Head and Neck Oncology Dataset (DAHNO) 10th annual report.

4 Blomberg M, Nielsen A, Munk C, Krüger Kjaer S. Trends in head and neck cancer incidence in Denmark, 1978-2007: focus on human papillomavirus associated sites. International Journal of Cancer 2011; 129(3): 733-741

5 Shu X, Ahlbom A, Feychting, M. Incidence Trends of Malignant Parotid Gland Tumors in Swedish and Nordic Adults 1970 to 2009. Epidemiology 2012; 23(5): 766-767

6 Boukheris H, Curtis RE, Land CE, Dores GM. Incidence of carcinomas of major salivary gland according to the WHO classification 1992-2006: a population based study in the United States. Cancer Epidemiol Biomarkers Prev.2009; 18(11): 2899-2906

7 Australian Institute of Health and Welfare 2014. Head and neck cancers in Australia. Cancer series 83. Cat. no. CAN 80. Canberra: AIHW.

8 Ellis GL, Auclair PL Tumours of the Salivary Glands. Washington DC: Armed Forces Institute of Pathology 1996. Atlas of Tumour Pathology, 3.

9 Estève J, Benhamou E, Croasdale M, Raymond L. Relative survival and the estimation of net survival: elements for further discussion. Statistics in Medicine 1990; 9(5):529-538

10 Coleman MP, Babb P, Damiecki P, Grosclaude P, Honjo S, Jones J, Knerer G, Pitard A, Quinn MJ, Sloggett A, De Stavola BL. Cancer survival trends in England and Wales, 1971-1995: deprivation and NHS Region. Studies in Medical and Population Subjects No. 61. London: The Office for National Statistics, 1999.

11 Bron LP, Traynor SJ, McNeil EB O'Brien CJ. Primary and metastatic cancer of parotid: comparison of clinical behaviour in 232 cases. Larygoscope 2003 Jun 113(6):1070-5

12 IARC – Chapter 5 Morphology code of the International Classification of Diseases for Oncology (ICD-O) and the Systematized Nomenclature of Medicine (http://snomed.org)

13 Barnes, E.L., Eveson, J.W., Reichart, P., Sidransky, D. Chapter 5, tumours of the salivary glands. In: World Health Organization Classification of tumours: pathology and genetics of head and neck tumours. IARC Press, Lyon, France; 2005:209–281.

14 Vos, Theo et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet 2015 Jun 386 (9995): 743-800

15 Mayne ST, Morse DE, Winn DM. Cancer Epidemiology and Prevention. New York: Oxford University Press 2006. Cancers of the Oral Cavity and Pharynx: 674–696.

16 Land CE, Saku T, Hayashi Y, Takahara O, Matsuura H, Tokuoka S, Tokunaga M, Mabuchi K. Incidence of salivary gland tumors among atomic bomb survivors, 1950–1987. Evaluation of radiation-related risk. Radiat Res. 1996;146:28–36.

Appendix

Table A Histological descriptions on site codes C07 and C08 and whether histology was included as primary salivary gland tumours (non-solid tumours were regarded as uncertain in origin). Individual histological code shown where numbers of cases over 10 and smaller numbers aggregated into similar types or high/low grade groups.

Code/s	Histology description	Histological group/grade	No. of cases	Primary
8140	Adenocarcinoma, NOS + 8572/8255	Adenocarcinoma	1718	Y
8070	Squamous carcinoma, NOS	SCC and variants	1668	N
8200	Adenoid cystic carcinoma	Adenoid cystic carcinoma	1508	Y
8430	Mucoepidermoid carcinoma	Mucoepidermoid carcinoma	1406	Y
8010	Carcinoma, NOS	Not classified	1375	N
8550/1	Acinic cell carcinoma	Acinic cell carcinoma	1164	Y
8000	Neoplasm, malignant	Not classified	585	N
8562	Epithelial-myoepithelial carcinoma	Other salivary variant	274	Y
8941	Carcinoma ex pleomorphic adenoma	Other salivary variant	254	Y
8071	Squamous cell carcinoma, keratinizing, NOS	SCC and variants	210	N
8147	Basal cell adenocarcinoma	Other salivary variant	133	Y
8940	Mixed tumor, malignant, NOS	Not classified	115	N
8500	Salivary duct carcinoma	Other salivary variant	99	Y
8020	Undifferentiated carcinoma	Other salivary variant	86	Y
8041	Small cell carcinoma, primary NOS	Other salivary variant/high	60	Y
8290	Oncocytic carcinoma	Other salivary variant/high	56	Y
8982	Malignant myoepithelioma (myoepithelial carcinoma)	Other salivary variant	46	Y
8260	Papillary adenocarcinoma, NOS	Other variants	43	N
8246	Neuroendocrine carcinoma	Other salivary variant/low	43	Y
8022	Pleomorphic carcinoma	Other variants	39	N
8012/3	Neuroendocrine carcinoma/large cell	Other salivary variant/high	39	Y
8021	Carcinoma, anaplastic NOS	Other variants	32	N
8032	Spindle cell carcinoma	SCC and variants	32	N
8980	Carcinosarcoma	Other salivary variant/high	30	Y
8082	Lymphoepithelial carcinoma	Other salivary variant/low	29	Y
8560	Adenosquamous carcinoma	SCC and variants	28	N
8480	Mucinous adenocarcinoma	Other salivary variant/low	26	Y
8310	Clear cell carcinoma, not otherwise specified	Other salivary variant/low	26	Y
8440	Cystadenocarcinoma/ low grade cribriform	Other salivary variant/low	25	Y
8481	Mucin-producing adenocarcinoma	Other variants	21	N
8525	Polymorphous low-grade adenocarcinoma	Other salivary variant	18	Y
8072	Squamous cell carcinoma, large cell, nonkeratinizing	SCC and variants	17	N
8561	Warthin tumor, malignant	Other salivary variant/low	16	Y
8800	Sarcoma, NOS	Not classified	13	N
8046	Non-small cell carcinoma	Other variants	13	N

Code/s	Histology description	Histological group/grade	No. of cases	Primary
8001	Tumour cells, malignant	Not classified	12	N
group	other 55 various histology codes	Other variants	122	N
group	histology codes: 8450/8201/8410	Other salivary variant/low	19	Y
group	histology codes: 8074/8083/8052/8075/8073	SCC and variants	17	N
group	histology codes: 8720/8123/8240	Not classified	15	N
Total - number of all cases included on major salivary gland anatomical sites C07 and C08			11432	